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| EXAMINER | |
|---|---|
| MYERS, CARLA J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1634 | |

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/608,397 | BECKER ET AL. | |
| | Examiner | Art Unit | |
| | Carla Myers | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-88 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-88 are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

***RESTRICTION***

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-26, 28-57, drawn to methods for identifying a polymorphism or set of polymorphisms associated with a A2M-mediated disease wherein the polymorphism is selected from the group consisting of one of the 13 polymorphisms set forth in the claims, classified in Class 435, subclass 6.

II. Claims 27 and 58, drawn to methods for genotyping a A2M protein or detecting a polymorphism in an A2M protein by determining the identity at one of the 3 polymorphic amino acid positions set forth in claim 21, classified in Class 435, subclass 4.

III. Claims 59-66, drawn to a method for identifying a compound that modulates alpha-2-macroglobulin activity, wherein the method comprises providing a cell that expresses the LRP receptor and contacting it with a candidate compound and a A2M protein having a polymorphism at position 14e, 20e or 30e, classified in Class 435, subclass 7.1.

IV. Claims 67 and 68, drawn to a method for identifying a compound that modulates alpha-2-macroglobulin activity, wherein the method comprises contacting an A2M protein having a polymorphism at position 14e, 20e or 30e with a test compound and with methylamine or amyloid beta and identifying a compound that modulates the activation of alpha-2-macroglobulin, classified in Class 435, subclass 7.1.

V. Claim 69, drawn to a method for making a pharmaceutical compound identified by a screening method using an A2M protein having a polymorphism at

position 14e, 20e or 30e, classified, for example, in Class 514, subclass 1 – note that further classification cannot be determined without additional information regarding the structure of the pharmaceutical compound.

VI. Claims 70-76, 81-84, 87 and 88, drawn to A2M nucleic acids, fragments and complements thereof comprising one of 13 polymorphisms set forth in the claims, and methods of expressing said nucleic acids, classified in Class 536, subclass 23.5 and Class 435, subclass 69.1.

VII. Claims 77-80, drawn to A2M proteins comprising one of 3 polymorphisms at positions 14e, 20e or 30e, classified in Class 530, subclass 350.

VIII. Claims 85 and 86, drawn to antibodies to A2M proteins comprising one of 3 polymorphisms at positions 14e, 20e or 30e, classified in Class 530, subclass 387.1.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I-V are drawn to patentably distinct methods requiring the use of different reagents, involving different process steps and having different outcomes or objectives. In particular, the method of invention I requires the use of nucleic acid primers, probes or sequencing reagents, and involves performing hybridization, amplification or sequencing methods in order to accomplish the objective of detecting a polymorphism or set of polymorphisms in the A2M gene as indicative of a polymorphism associated with a neurodegenerative disorder or as indicative of Alzheimer's disease. The method of invention II requires the use of protein sequencing and detection reagents and involves performing method steps of sequencing a protein or detecting a polymorphism in a protein using an antibody in order to accomplish the objective of

detecting a polymorphism in an A2M protein as indicative of the presence of a polymorphism associated with a neurodegenerative disorder or as diagnostic of Alzheimer's disease. Invention III requires the use of cells expressing the LRP receptor and test compounds and involves contacting cells expressing the LRP receptor with a test compound and with an A2M protein having a polymorphism in order to accomplish the objective of identifying a compound that modulates A2M activity. The method of invention IV requires the use of A2M polypeptides having a polymorphism, test compounds and methylamine and involves contacting A2M polypeptides with methylamine and with a test compound in order to accomplish the objective of identifying test compounds that modulate the formation of a complex between A2M and amyloid-beta. The method of invention V requires the use of a compound that modulates A2M activity and involves incorporating this compound into a pharmaceutical composition. Accordingly, the methods of inventions I-V are patentably distinct from each other.

Inventions I and VI and inventions V and VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. 806.05(h)). In the instant case, the nucleic acids of invention VI can be used in a materially different process, such as for synthesizing nucleic acids or proteins.

Inventions I and VII and V and VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP 806.04, MPEP 808.01). In the instant case, the proteins of inventions VII are not required to practice the detection methods of inventions I or V.

Inventions I and VIII and V and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP 806.04, MPEP 808.01). In the instant case, the antibodies of inventions VIII are not required to practice the detection methods of inventions I or V.

Inventions II and VI, III and VI and IV and VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP 806.04, MPEP 808.01). In the instant case, the nucleic acids of inventions VI are not required to practice the detection methods of inventions II, III or IV.

Inventions II and VII, III and VII and IV and VII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. 806.05(h)). In the instant case, the proteins of invention VII can be used in a materially different process, such as for synthesizing antibodies.

Inventions II and VIII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. 806.05(h)). In the instant case, the antibodies of invention VIII can be used in a materially different process, such as for isolating proteins or for therapeutic purposes.

Inventions III and VIII and IV and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP 806.04, MPEP 808.01). In the instant case, the antibodies of inventions VIII are not required to practice the detection methods of inventions III or IV.

Inventions VI and VII are patentably distinct in structure and physicochemical properties. Inventions VI is drawn to nucleic acids whereas inventions VII is drawn to proteins. Because nucleic acids are composed of nucleotides and proteins are composed of amino acids, the inventions have different structural and functional properties. Furthermore, the products are utilized in different methodologies, such that nucleic acids may be utilized in hybridization assays, while proteins may be utilized in ligand binding assays or to generate antibodies. Synthesis of the proteins of invention VII do not require the particular products of the nucleic acids of inventions VI since the proteins can be isolated from natural sources or chemically synthesized.

Inventions VI and VIII are patentably distinct in structure and physicochemical properties. Invention I is drawn to nucleic acids whereas invention VIII is drawn to antibodies. The nucleic acids and antibodies differ in their structure, function and effect. While the nucleic acids of invention VI consist of nucleotides, the antibodies of invention VIII encompass 2 heavy chains and 2 light chains containing constant and variable regions, including framework regions which act as a scaffold for the 6 CDRs that function to bind an epitope. The nucleic acids and antibodies also have different functional properties and can be utilized in different methodologies, such that nucleic acids may be used in hybridization methods, whereas antibodies may be used in protein binding methods. Synthesis of the antibodies of inventions VIII does not require the particular products of the nucleic acids of inventions VI since the antibodies can be isolated from natural sources or chemically synthesized.

Inventions VII and VIII are patentably distinct in structure and physicochemical properties. Invention VII is drawn to proteins whereas invention VIII is drawn to antibodies. The proteins and antibodies differ in their primary amino acid sequence and in the secondary and tertiary structures. While the protein of invention VII is a single chain molecule, the antibody of invention III encompasses 2 heavy chains and 2 light chains containing constant and variable regions, including framework regions which act as a scaffold for the 6 CDRs that function to bind an epitope. The proteins and antibodies also have different functional properties and can be utilized in different methodologies. Synthesis of the antibodies of inventions II does not require the particular products of the proteins of inventions VII since the antibodies can be isolated

from natural sources or chemically synthesized. Further, antibodies which bind to an epitope of the protein of group II may be known even if the protein is novel.

4. These inventions are distinct for the reasons given above and have acquired a different status in the art as demonstrated by their different classification and recognized divergent subject matter. Further, inventions I-VIII require different searches that are not co-extensive. For instance, a literature and sequence search for the nucleic acids of invention VI is not co-extensive with a literature and sequence search for the proteins of invention VII or the antibodies of invention VIII or a search for the methods of inventions I-V. Additionally, a search for each of the methods of inventions I-V is not co-extensive with one another. For instance, a keyword / literature search for methods of detecting a mutation in an A2M protein as diagnostic of a disorder (invention II) would not be co-extensive with a keyword / literature search for methods for identifying compounds that modulate A2M proteins (inventions III and IV) or methods of making a pharmaceutical composition (invention V). Further, a finding that the method of invention I is anticipated or obvious over the prior art would not necessarily extend to a finding that the method of inventions II-V were also anticipated or obvious over the prior art. Similarly, a finding that the method of invention I is novel and unobvious over the prior art would not necessarily extend to a finding that the methods of invention II-V are also novel and unobvious over the prior art. Accordingly, examination of these distinct inventions would pose a serious burden on the examiner and therefore restriction for examination purposes as indicated is proper.

5. **Polymorphism / Sequence Election Requirement Applicable to Inventions I-VIII**

The claims have been presented in improper Markush format, as distinct products and distinct methods are improperly joined by the claims. Inventions I-VIII read on patentably distinct inventions drawn to multiple nucleic acid, protein and antibody sequences. The claims encompass polymorphic variants and haplotypes of the A2M gene, the A2M protein and antibodies to said proteins. The 16 polymorphisms set forth in the claims consist of distinct nucleotide sequences, and a further restriction is applied to each invention. Applicants must elect a single polymorphism or one haplotype (i.e., group/set of polymorphisms) to be examined. Further, with respect to inventions VI, VII and VIII, the response should indicate the SEQ ID NO corresponding to the elected polymorphism.

It is noted that each of the polymorphic variants and combinations of polymorphisms constitute distinct chemical compounds and each has a distinct functional property. The chemical structure of each polymorphism and of each molecule containing the polymorphism is distinct from each of the other polymorphisms. For example, a polynucleotide comprising, for instance, the polymorphism 6i is chemically, structurally and functionally distinct from a polynucleotide comprising the polymorphism 12i.1. Further, a search for a nucleic acid comprising the polymorphism 6i would not be co-extensive with a search for a nucleic acid comprising the polymorphism 12i.1. Each of the haplotypes (sets of polymorphisms) is also distinct from the individual polymorphisms and from one another. Each of the haplotypes infers a distinct biological property to an organism that is distinct form that of other haplotypes. Additionally, a reference which renders obvious a single polymorphism or haplotype will

not necessarily also render obvious a different polymorphism or haplotype. Similarly, a search indicating that a particular haplotype is novel or unobvious would not extend to a holding that a single polymorphism or a different haplotype is also unobvious.

Accordingly, the nucleic acid, protein and antibody sequences containing the polymorphisms or haplotypes are thus deemed to constitute independent and distinct inventions within the meaning of 35 U.S.C. 121. Absent evidence to the contrary, each such nucleotide, protein and antibody sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.14. Applicant is advised that this is a restriction requirement and should **not** be construed as an election of species.

6. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. 1.48(b) and by the fee required under 37 C.F.R. 1.17(h).

8. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the

limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
October 18, 2005

CARLA J. MYERS
PRIMARY EXAMINER